REMARKS

This Reply is submitted in response to the final Office Action dated June 19, 2001. Entry of the amendments and remarks made herein is respectfully requested pursuant to 37 CFR §1.116(b), in that the amendments and evidence submitted simplify the issues for appeal. While Applicants are hopeful that the evidence and arguments presented will cause the Examiner to re-evaluate her position, if the Examiner is not willing to negotiate acceptable claim language or allow the present claims on the basis of this evidence, Applicants respectfully request that she at least enter the material into the file so that the Board may have access to all the relevant information on appeal.

New claims 34 and 35 were added above in order to define the claimed protein according to the structural characteristics disclosed in the specification. Support for these claims may be found at page 9, first full paragraph. No new matter has been added.

Claims 4-10 and 22-33 stand rejected under 35 U.S.C. §101 as allegedly lacking a specific, substantial and credible utility or a well-established utility. A corresponding rejection has been made under the enablement provision of first paragraph of §112, because one skilled in the art would allegedly not know how to use the claimed invention due to the alleged lack of utility. Applicants respectfully traverse these rejections.

Applicants maintain their arguments of record with regard to the utilities disputed thus far. However, applicants traverse in particular on the following grounds. The Examiner has dismissed the noted homology of the claimed proteins to the TGF-ß superfamily as failing to provide the requisite utility, apparently because the biological activities of this family are "diverse." The Examiner further alleges that it could not have been predicted which activity GDF-1 would have, if any (see the Office Action, 6-19-01 at page 4, and the Office Action dated 2-22-99 at the paragraph bridging pages 4-5).

According to the comments and answers recently published in the Federal Register with the new utility examination guidelines (FR, Vol. 66, No. 4, January 5, 2001), it is perfectly acceptable to assert a specific, substantial and credible utility on the basis of "homology to existing nucleic acids or proteins having an accepted utility." Furthermore, according to this Notice, a rigorous correlation is not necessary; only a "reasonable" correlation (see the FR Notice, page 1096, middle column continuing into right-hand column). As stated therein, "When a class of proteins is defined such that the members share a specific, substantial, and credible utility, the reasonable assignment of a new protein to the

class of sufficiently conserved proteins would impute the same specific, substantial, and credible utility to the assigned protein" (with emphasis). Id.

According to the new utility guidelines, "the asserted utility must be accepted by the examiner unless the Office has sufficient or sound reasoning to rebut such an assertion" (with emphasis) Id. The Examiner rejects the asserted utility on the basis that the members of the TGF-ß family exhibit diverse activities. However, the Examiner provides no evidence that those of skill in the art at the time the invention was made would have believed that members of the superfamily exhibit such diverse activities as to preclude prediction of function. In fact, according to an abstract by Akhurst published in 1990 (just prior to the effective filing date of the application) and attached hereto, there had been five type beta transforming growth factors (TGF betas) identified at that time, each of which was found to play "a pivotal role in embryonic processes." Furthermore, according to Akhurst et al., there was sufficient evidence to assign TGF beta 1, beta 2 and beta 3 a role in mammalian developmental processes, including control of growth, differentiation, tissue induction and morphogenesis.

Thus, at the time the invention was made in 1990, one of skill in the art would have reasonably predicted that a member assigned to the TGF-ß superfamily would play a role in embryonic development, and in the growth and differentiation of tissues, given that the five members identified at that time were shown to play a pivotal role in embryonic development. Indeed, according to the instant specification at page 1, "a growing number of polypeptide factors playing critical roles in regulating differentiation processes during embryogenesis [had] been found to be structurally homologous to transforming growth factor ß." On that basis, and in view of the homology of GDF-1 to TGF-ß, the present inventor predicted that the GDF-1 protein was likely to play an important role in mediating developmental decisions related to cell differentiation (see page 2, lines 25-29). Moreover, it was perfectly reasonable on the basis of that prediction and the homology demonstrated to assert that the claimed protein would find utility in prenatal screens to detect developmental abnormalities, as disclosed on pages 12-13 of the specification.

The Examiner has provided no evidence to suggest that these predictions, which were based on the known activities of TGF-ß at the time, were unreasonable. She has presented no evidence to suggest that TGF-ß activities were thought to be so diverse at that time so as to make these predictions unreasonable. Furthermore, the argument that one could not have predicted the role of the GDF-1 protein based on homology with this superfamily should be

re-evaluated in view of recent evidence with GDF1-/- knock-out mice that demonstrates that, in fact, Applicant's predictions were correct.

For instance, as the present inventor and others have shown in a recently published paper (Rankin et al., 2000, Regulation of left-right growth patterning in mice of growth/differentiation factor-1, Nature Genetics 24: 262-66), GDF-1 plays a pivotal role in embryogenesis. A knockout mouse was generated in order to examine the biological function of GDF-1, which exhibited a spectrum of defects related to left-right axis formation in embryos, including misplacement of internal organs (Fig. 2), developmental defects in organs and cardiac abnormalities (Fig. 3). The authors concluded that these findings indicate that GDF-1 is essential for proper establishment of the left-right axis in mice, and is required for the expression of many genes expressed downstream from gdf1 during development.

Thus, results with the GDF1-/- knockout mouse prove that GDF-1 is required for the proper development and positioning of organs during embryogenesis. This is consistent with the function of GDF-1 predicted in the specification (page 2, lines 25-29), and the results in the specification showing the expression of GDF-1 during embryogenesis (see Example 4 and Fig. 6). These results also suggest that the asserted utility of GDF1 in prenatal screens for abnormal development is a reasonable utility for the disclosed protein, given that aberrant expression of GDF-1 has now been shown to have significant and substantial effects on embryonic development.

Applicants' assignment of GDF-1 to the TGF-ß superfamily has been substantiated by the numerous GDF proteins that have been subsequently identified and likewise assigned to this superfamily. Thus, others of skill in this art have followed Applicant's lead, and have corroborated that classification (see the attached PubMed printout of scientific abstracts published after the present invention was filed). In contrast, the Examiner has presented no evidence that GDF-1 should not be classified in the TGF-ß family. Furthermore, it is pertinent to point out that numerous other GDF proteins have been patented on the basis of their homology with the TGF-ß superfamily. See, e.g., USP 5,808,007 (GDF-3); USP 5,801,014 (GDF-5); USP 5,770,444 (GDF-6); USP 5,986,058 (GDF-7); USP 5,827,733 (GDF-8); USP 5,821,056 (GDF-9); USP 5,831,054 (GDF-12); USP 6,120,760 ("Growth and Differentiation Factors of the TGF-ß Superfamily"). Thus, Applicants respectfully stress again that it appears they are being held to a different standard than others have been held to before.

Thus, it is clear from the issued patents noted above that members of the TGF-ß superfamily, including GDF proteins, have a well-established utility. Furthermore, at the time the application was filed, the TGF-ß superfamily was known to comprise proteins involved in embryonic development, a function that Applicants predicted that GDF-1 would share. Further, Applicants have now shown that GDF-1 does possess the predicted function, thereby supporting the disclosed utilities, i.e., use in prenatal screening for developmental defects. And as noted above, according to the new utility examination guidelines, it is perfectly acceptable to predict a specific, substantial and credible utility on the basis of homology to existing nucleic acids or proteins having an accepted utility.

As acknowledged in the Office Action, GDF-1 proteins are 26-52% similar to TGF-ß family members on the amino acid level. Moreover, according to the specification at the paragraph bridging pages 19-20, GDF-1 contains all of the invariant amino acids present in the C-terminal 122 amino acids of other TGF-ß superfamily members, including the seven characteristic cysteine residues as well as many of the other most highly conserved amino acids. For instance, like the other family members, the C-terminal portion of the predicted GDF-1 polypeptide is preceded by a pair of arginine residues at positions 236-37. Thus, GDF-1 contains sufficient homology to be assigned to the TGF-ß superfamily, as substantiated by the similar assignment of other GDF proteins.

Thus, given that the new utility examination guidelines explicitly state that it is permissible to assert a credible utility on the basis of homology to a family of proteins having a well-established utility, and given that the inventors predicted and have now proven that GDF-1 would share the utility that had been well-established for members of the TGF-ß superfamily at the time the application was filed, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §101 and the enablement provision of §112, first paragraph.

Claims 4-7, 22, 24, 25 and 30 were also rejected under the written description section of 35 U.S.C. §112, first paragraph. According to the Office Action (page 5), the specification discloses human and mouse GDF-1, but indicates that they have less conservation across species (69%) than other TGF-ß family members. Further, the Examiner alleges that no structural features were identified that could be used to define a GDF-1 protein, and the application teaches no assays for functional identification. Applicants respectfully traverse the rejection.

First, while it is true that human and mouse GDF-1 are 69% identical through the entire length of the proteins, the specification also discloses that these two genes are 87% identical in the region beginning with the first conserved cysteine and extending to the C-terminus (see page 31, lines 19-20). Thus, this specific domain of GDF-1 is more highly conserved across species, and would constitute a structural feature for identifying a GDF-1 protein.

Furthermore, the instant specification does disclose an assay for identifying a GDF-1 gene, in that a probe generated from the full length murine open reading frame of GDF-1 hybridized specifically to the human gene in Southern hybridization (see Fig. 14 legend at page 9, and the relevant discussion at pages 31-32). As also shown in Figure 5, even at high stringency, a murine GDF-1 probe identified a single prominent band in both human and hamster genomic DNA. In this regard, Applicants note that new claims 34 and 35 have been submitted above, which define the claimed protein according to its coding DNA sequence, as identified by the hybridization assay disclosed in the specification.

Given the extent of homology between human and mouse GDF-1 shown in the specification, and the fact that probes generated from these sequences cross-hybridize specifically to the GDF-1 gene in other species using hybridization conditions specifically defined in the disclosure, it would be clear to those skilled in the art upon reading the present disclosure that Applicants were in possession of the claimed invention at the time the application was filed.

All issues raised by the Office Action dated June 19, 2001, have been addressed in this Reply. Accordingly, a Notice of Allowance is next in order. If the Examiner has any further questions or issues to raise regarding the subject application, it is respectfully

requested that she contact the undersigned so that such issues may be addressed expeditiously.

Respectfully submitted,

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